# ATENT COOPERATION TRI .TY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2004/031617 | 23.09.2004 | 23.09.2003 |

International Patent Classification (IPC) or both national classification and IPC
C07K14/47, C12Q1/68, G01N33/574

Applicant
CHIRON CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/031617



**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. II Priority**

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 31, 32, 35-37 and 50-54

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 31, 32, 35-37 and 50-54

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

## Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-30, 33, 34, 38-49 and 55 (all partially)

## Box No. V Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | |
| | No: | Claims | 1-30, 33, 34, 38-49 and 55 (all partially) |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-30, 33, 34, 38-49 and 55 (all partially) |
| Industrial applicability (IA) | Yes: | Claims | 1-30, 33, 34, 38-49 and 55 (all partially) |
| | No: | Claims | |

2. Citations and explanations

   **see separate sheet**

## Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)**

International application No.
PCT/US2004/031617



**Re Item IV.**

The separate inventions/groups of inventions, all related to claims 1-30, 33, 34, 38-49 and 55 (all partially, see below) are:

1 Nucleic acid arrays comprising at least two nucleic acids, one of which comprises at least 10 contiguous nucleotides of SEQ ID NO: 5, while the other comprises at least 10 contiguous nucleotides of any of the sequences listed in claim 1; methods of diagnosing cancer comprising determining the level of expression of a nucleic acid of SEQ ID NO: 5.

2 Peptide arrays comprising at least two polypeptides, one of which is encoded by any open reading frame within SEQ ID NO: 4, while the other is encoded by any open reading frame within any of the sequences listed in claim 4.

3 Peptide arrays comprising at least two polypeptides, one of which is encoded by SEQ ID NO: 5, while the other is encoded by any of the sequences listed in claim 5.

4 Peptide arrays comprising at least two polypeptides, one of which is SEQ ID NO: 6 and the other is any of the sequences listed in claim 6.

5 Antibodies or fragments thereof that bind polypeptides derived from SEQ ID NO: 4; hybridomas producing them; kits and pharmaceutical compositions comprising them.

6 Methods of detecting the presence of cancer cells using antibodies against polypeptides derived from SEQ ID NO: 4

7 Kits comprising at least two nucleic acids, one of which hybridizes to a nucleic acid derived from SEQ ID NO: 4

8 Kits comprising at least two nucleic acids, one of which hybridizes to a nucleic acid derived from SEQ ID NO: 5

9 Methods of screening for anticancer activity using cells expressing a gene encoded by SEQ ID NO: 4

10 Methods of screening for anticancer activity using cells expressing a gene encoded by SEQ ID NO: 5

11 Methods of diagnosing cancer comprising determining the level of expression of a polypeptide of SEQ ID NO: 6

12 Methods of detecting cancer comprising detecting the level of activity of a polypeptide of SEQ ID NO: 6

13 Methods of detecting cancer comprising detecting the level of antibodies against a polypeptide of SEQ ID NO: 6

14 Methods of screening for anticancer drugs capable of modulating the activity of a

protein encoded by SEQ ID NO: 5

15 INVENTIONS 15 TO 448:
Methods and products for the diagnosis and treatment of cancer based on gene 1-007 and its gene products (SEQ ID NOS: 7-12; Table 125).

[idem for each one of the remaining genes listed in Table 125]

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The common concept disclosed in the application, as defined by the present claims, can be considered as the provision of products and methods for the diagnosis and treatment of cancer based on detection of expression levels of cancer-associated (CA) genes and gene related products.

However, this concept is well known in the field since more than 20 years. Augenlicht and Kobrin, for example, disclosed in 1982 the identification of 55 genes whose expression is altered in colon tumors (see Abstract and Table 3). Since then, hundreds of documents, some of them cited as examples in this ISR, publish the results of expression profiling analysis of tumor samples leading to the identification of diagnostic markers and therapeutic targets. The strategy had become common practice in the field of molecular medicine at the date of priority.

In view of this prior art, the problem to be solved by the present invention can be considered as the provision of further cancer-associated genes and gene related products. The solutions given by the present application are the genes corresponding to the nucleotide and protein sequences listed in the claims and summarized in Table 125. This ISA is of the opinion that there is no single inventive concept underlying these groups of inventions in the sense of rule 13.1 PCT.

No other technical features can be distinguished which, in view of the prior art could be regarded as special technical features in the sense of Rule 13.2 PCT. The description and examples do not provide either for a novel and inventive unifying concept for the present inventions. The technique used by the inventors to identify the cancer associated genes of the present application was known to the skilled person well before the date of priority: Berns reviews already in 1988 how provirus tagging is used by researchers as an instrument to identify oncogenes.

The idea of combining at least two CAs in products or methods for detection of cancer was also well known at the date of priority, since all expression profiling efforts are based on the simultaneous detection of multiple gene expression markers (see for example US2003/022237, paragraph [252]). Consequently, even if such feature was shared by all claimed inventions, which is not the case, it would not be considered a special technical feature.

Consequently, there is a lack of unity, the methods and products corresponding to each one of these genes gives rise to one group of inventions which does not share a common inventive concept with any of the others.

Considering now the first group of inventions, i.e. the methods and products for the diagnosis and treatment of cancer based on gene 1-004 (SEQ ID NOS: 1-6; Table 125), the common concept within this group can be considered as the provision of products and methods for the diagnosis and treatment of cancer, based on gene 1-004 and its derived products.

However, this concept is not new in view of WO03/008583, which discloses methods and products for diagnosing and treatment of cancer based on gene 1-004 (gene CCR7; see Abstract, claim 11, Table 6 and SEQ ID NO: 19 to 24).

In view of this prior art the problem to be solved by this first group of inventions can be considered as the provision of further products and methods for the diagnosis and treatment of cancer based on gene 1-004. The solutions given by the present application are the products and methods listed in the claims, namely: nucleic acid arrays, peptide arrays, antibodies and hybridomas, pharmaceutical compositions, methods of diagnosis, methods of treatment, electronic libraries, and methods of screening for anticancer compounds.

Because no other technical features can be distinguished which, in view of the prior art could be regarded as special technical features in the sense of Rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying these inventions in the sense of rule 13.1 PCT. Consequently, there is a lack of unity, the methods and products claimed not belonging to a common inventive concept (see above, list of non-unitary inventions).

**Re Item V.**

Document by Affymetrix Inc.(11.03.2002) discloses a nucleic acid array *suitable* for detecting a cancer associated nucleic acid comprising at least two nucleic acids, one of which comprises at least 10 contiguous nucleotides of SEQ ID NO: 5 (see probe 206337_at), while the other comprises at least 10 contiguous nucleotides of SEQ ID NO: 11 (see probe 221455_s_at).

Document WO03/008583 discloses methods of diagnosing cancer comprising determining the level of expression of a nucleic acid of SEQ ID NO: 5 (gene CCR7; see Abstract, claim 11, Table 6 and SEQ ID NO: 19 to 24).

Therefore, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-30, 33, 34, 38-49 and 55 insofar they refer to Invention 1, is not new in the sense of Article 33(2) PCT.